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WO 01/04098 A1

(54) Title: PROCESS OF MAKING IMIDAZOLIDINE-2-ONE DERIVATIVES

(57) Abstract: The invention relates to the process of making imidazolidine-2-one derivatives comprising the reaction of ephedrine derivatives with urea in the presence of ammonium sulfamate.

PROCESS OF MAKING IMIDAZOLIDINE-2-ONE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to a process to prepare chiral auxiliary intermediates which are useful in the asymmetric syntheses of useful organic compounds. These auxiliaries are imidizolidin-2-ones. Of particular importance, the present invention relates to any improvement in the process to prepare aromatic ring-fused cyclopentane derivatives, specifically indane-2-carboxylates and cyclopentano[b]pyridino-2-carboxylates. This improvement relates to the process for preparing important chiral intermediates used in the preparation of indanes and cyclopentano[b]pyridines. This chiral intermediate is (4R,5S)-1,5-dimethyl-4-phenyl-imidizolidin-2-one.

BACKGROUND OF THE INVENTION

Intermediates that are useful in asymmetric synthesis to produce an asymmetric center are very important to organic chemistry in general and, specifically, within the pharmaceutical field. The term chiral auxiliary means a non-racemic functional group that imparts a distereoselective reaction at a remote prochiral center of a molecule. Chiral auxiliary intermediates which are useful in such synthesis are known in the art. These include 1,3-oxazolidin-2-ones, see Soloshonok et al., ***Org. Letters,*** 747(2000) and reviews noted therein, and imidiazolidin-2-ones, see Bongini et al., ***Tetrahedron: Asymmetry,*** 1996, 1457 and references therein. All information within these references necessary to understand and use this invention are incorporated by reference.

The chiral intermediate (4R,5S)-1,5-dimethyl-4-phenyl-imidizolin-2-one is one of these important auxiliaries useful to prepare pharmaceutically active compounds. Other structurally related iminidazolin-2-ones, including its enantiomer, are also useful. The known literature procedures to make these compounds have a number of problems. An improved method to prepare these auxiliaries was desired. I have now found and disclose useful improvements to the process to prepare these clinical auxiliary intermediates.

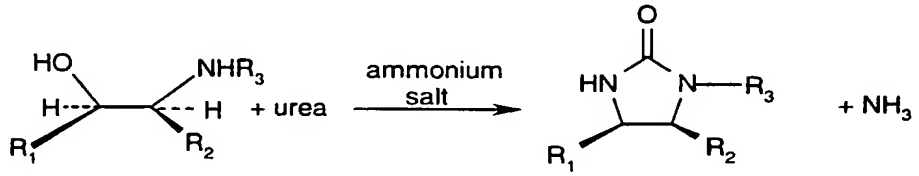
More specifically, these process improvements can be used to prepare certain endothelin receptor antagonists. Certain indane-2-carboxylic acids and cyclopentano[6]pyridines are useful endothelin receptor antagonists; see U.S. Patent Nos. 5,817,693; 5,716,984 and 5,389,620. The racemates of these compounds have important pharmaceutical activity; however, the enantiomers have improved activity. For example, (+)(1S,1R,3S)-3-[2-hydroxyeth-1-yloxy)-4-methoxyphenyl]-1-[3,4-methylenedioxyphenyl)-5-propoxylindane-2-carboxylic acid and (+)(1S,2R,3S)3-(2-carboxymethoxy-4-methoxyphenyl-1-(3,4-methylene dioxyphenyl)-5-propoxylindane-2-carboxylic acid are under development and are potential commercial products.

In a PCT application published on May 15, 1997 under International Publication No. WO 97/17342, an improved process for preparing these enantiomers is described. The imidizolidin-2-one chiral intermediate was disclosed as an important chiral auxiliary intermediate in this process.

Synthesis of this intermediate is reported in the literature by condensing urea with ephedrine; see Close, ***J. Org. Chem., 15***, 1131 (1950) and Drewes et al., ***Chem Ber. 126***, 2663 (1993). This literature procedure has several problems associated with it. The yield is lower than is desired for a commercial process. The process also gives an undesirable oxazolidin-2-one impurity as 25-30% of the crude isolated product. Purification is required before the product can be used. In addition, certain by-products, such as ammonium chloride, cyanuric acid and ammonia form solid particulates that tend to block risers in certain fixed vessels and poses a safety hazard. I have found, discovered and disclose in this application an improved process which overcomes the problems associated with the known method.

SUMMARY OF THE INVENTION

The process of this invention involves the following process:



IA IIA

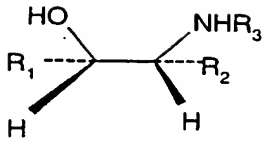
wherein:

R_1 is C_{1-8}alkyl, cyclohexyl, phenyl, phenyl substituted with C_{1-6}alkyl, halo, nitro, C_{1-6}alkoxy, C_{1-6}alkylmercapto or CF_3, napthyl or napthyl substituted with C_{1-6}alkyl, halo, nitro, C_{1-6}alkoxy or CF_3;

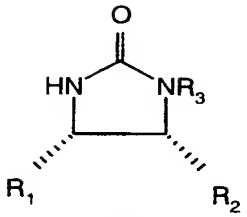
R_2 is C_{1-8}alkyl, C_{1-8}alkenyl, cyclohexyl, phenyl, or phenylC_{1-6}alkyl wherein each phenyl may be substituted with one or two substituents selected from nitro, C_{1-6}alkoxy, methylenedioxy or CF_3; and

R_3 is C_{1-12}alkyl, C_{1-8}alkenyl, C_{3-6}cycloalkyl, phenyl or phenylC_{1-6}alkyl wherein each phenyl may be substituted with one or two substituents selected from nitro, C_{1-6}alkyl, halo, nitro, C_{1-6}alkoxyl, methylenedioxy, CF_3 or dialkylamino, and urea together in the presence of a non-volatile ammonium salt.

The process of this invention proceeds equally with the enantiomer of compound IA (compound IB) to produce the enantiomer of the product IIA (compound IIB). The structures of compounds IB and IIB are as follows:



I B



II B

wherein R_1, R_2 and R_3 are as defined above. The chiral auxiliaries defined by compound IIB are also useful in asymmetric synthesis of useful organic compounds.

Within R_1, a preferred group are those moieties which provide steric bulk such as phenyl, substituted phenyl, napthyl and substituted napthyl. Particularly preferred is phenyl. A wider variety of groups are equally useful in this process within R_2 and R_3. Preferred R_2 and R_3 groups are alkyl, phenyl or phenylalkyl. Within R_1, R_2 and R_3, halo means fluoro, bromo or chloro and alkyl means straight or branched chained alkyl groups.

Compounds of Formula I are commercially available or readily prepared by one skilled in the art by known methods. L-ephedrine, a compound of Formula IA where R_1 is phenyl and R_2 and R_3 are methyl, and D-ephedrine, the related compound of Formula IB, are readily available and cheap compounds which is particularly useful in this process.

The process is carried out in the presence of a non-volatile ammonium salt at a high temperature. Suitable ammonium salts include, but are not limited to, ammonium sulfamate, ammonium sulfate, and ammonium dihydrogen phosphate. Other suitable ammonium salts can be readily determined by one skilled in the art. A preferred ammonium salt is ammonium sulfamate.

The process is run at a temperature of 75°-190°C. The reaction is run in the beginning in an inert organic solvent with a boiling point greater than 75°C in order to provide efficient stirring of the melting reactants. Examples of suitable solvents include, but are not limited to, benzene, toluene, xylene, mesitylene, chlorobenzene and the like. After the reaction is heated to the boiling point of the solvent, it is allowed to distill off. The reaction melt is heated to 160°-190°C until the reaction is completed.

The ratio of reactants is at least 1:1:1 equivalents of urea: compound of Formula I: ammonium salt. A preferred ratio is 3:1:1 equivalents.

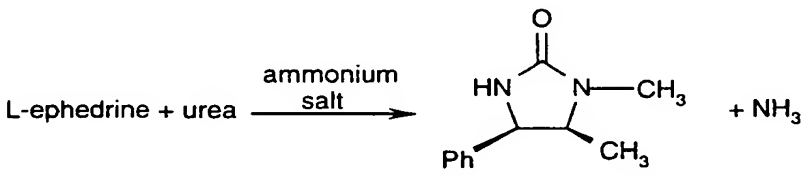
The reaction vessel is charged with the reactants and then is purged with nitrogen before heating is begun. During the reaction, ammonia begins to evolve when the reaction mixture reaches a temperature of about 100° or greater. Ammonia can be collected by use

of an acid scrubber. Evolution of the ammonia should be monitored and controlled at a reasonable rate by the rate of heating of the reaction mixture.

Work-up of the process by the addition of water results in compound of Formula II in high enantiomeric purity and with minimum amounts of the undesired oxazolidin-2-one impurity. The compound of Formula II can be used directly without additional purification.

A particularly preferred process of this invention is the preparation of the compound (4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2-one (compound of Formula IIIA). This compound is referred to as the most preferred chiral auxiliary in WO 97/17342 and is a critical intermediate in the stereoselective process disclosed and claimed in WO 97/17342. The entire published application of WO 97/17342 is incorporated by reference into this application.

The process to prepare this compound is as follows:



III A

The process is carried out in the presence of the non-volatile ammonium salt at a temperature of 90° to 190°. The reaction is run at the beginning in an inert organic solvent with a boiling point greater than 75°C in order to provide efficient stirring of the melting reactants. Examples of suitable solvents include, but not limited to, benzene, toluene, xylene mesitylene, chlorobenzene and the like. The ratio of reactants urea: L-ephedrine:ammonium salt is 3:1:1 equivalents.

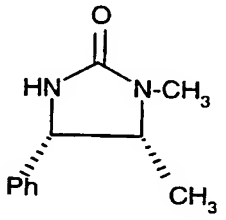
The reaction vessel is purged with nitrogen before heating is begun. During the reaction, ammonia begins to evolve when the reaction mixture reaches a temperature of about 140°. Ammonia can be collected by use of an acid scrubber. Evolution of the ammonia should be monitored and controlled at a reasonable rate by the rate of heating of the reaction mixture.

After the reaction is heated to about 100° or the boiling point of the solvent, the solvent is allowed to distil off and the reaction melt is heated to 160-190°C, preferably 165-180°C, until the reaction is completed. The most preferred temperature range is 175-179°C.

Work-up with water results in compound III in greater than 99.9% enantiomeric purity and an overall yield improvement of 10-25% over published processes. In addition, the oxazolidinone impurity obtained with the older published procedure is produced in less than 1%.

Compound III can be used directly as obtained in the process to prepare the desired pharmaceutically important compounds, for example, as used within the process disclosed in WO 97/17432.

The use of D-ephedrine in the particularly preferred process above produces the compound of Formula IIIB.



III B

This compound is useful in the preparation of a number of useful pharmaceutical compounds.

Another advantage of the chiral auxiliaries produced by the process of this invention is that they can be recovered from the asymmetric synthesis and reused. This results in greater economical efficiencies.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description and the Examples that follow, utilize the present invention to its fullest extent. The following Examples are to be construed as merely illustrative and not a limitation of the scope of the present invention.

EXAMPLE 1

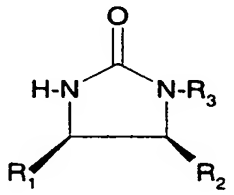
(4R,5S)-1,5-Dimethyl-4-phenyl-imidazolidin-2-one

To a 20 gallon glass-lined reactor was added toluene (36 L), urea (16.4 kg, 273.3 moles, 3 equiv), ammonium sulfamate (10.35 kg, 92.3 moles, 1 equiv) and L-ephedrine (14.36 kg, 86.9 moles, 1 equiv.). The reaction vessel was purged with nitrogen then was heated to 98°C to remove the toluene. After 40 minutes, all 36 L of toluene was distilled. The reaction was heated to 175°C. Ammonia begins to evolve at ~140°C. After 1.5 hours at 175°C to 180°C, HPLC indicated that the reaction had proceeded to completion. The reaction vessel was cooled to about 105°C and quenched with 27 L of water. At 57°C, 3 L of ethanol was added. The reaction, as a slurry, was stirred at ambient temperature for 4 hours then was transferred to a basket centrifuge and collected. The centrifuged wet cake was rinsed with 60 L of water and collected to yield 11.65 kg of wet cake. The wet cake was dried under vacuum at 20 – 25 °C for 14 hours. The final dry weight of crude product

was 10.7 kg (56.25 moles, 65% crude yield). This material was recrystallized from acetonitrile:water (93:7): m.p. 174-175°C;][α]25/D –96.3° (c 1.0, CH_2C1_2); [α]25/D –46° (c 1.0, MeOH).

EXAMPLES 2-5

Following the procedures set forth in this specification and of Example 1, the following chiral auxiliaries are prepared.



IIIA

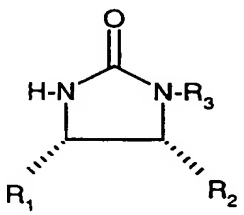
Example	R_1	R_2	R_3
2	2,5-dimethoxyphenyl	CH_3	t-butyl
3	4-hydroxyphenyl	CH_3	4-hydroxyphenyl-2-ethyl
4	phenyl	CH_3	3-(3-methoxyphenyl)-3-oxo-propyl
5	4-isopropylmercaptophenyl	CH_3	n-octyl

EXAMPLE 6

Substituting D-ephedrine for L-ephedrine in the procedure of Example 1 yields the compound (4S,5R)-1,5-dimethyl-4-phenylimidazolidin-2-one.

EXAMPLES 7-10

Following the procedures set forth in this specification and of Example 1, the following chiral auxiliaries are prepared.

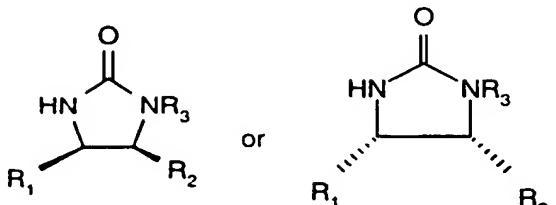


IIIB

Example	R_1	R_2	R_3
7	2,5-dimethoxyphenyl	CH_3	t-butyl
8	4-hydroxyphenyl	CH_3	4-hydroxyphenyl-2-ethyl
9	phenyl	CH_3	3-(3-methoxyphenyl)-3-oxo-propyl
10	4-isopropylmercaptophenyl	CH_3	n-octyl

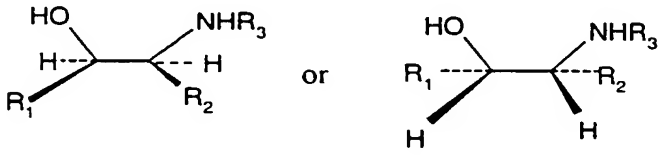
What is claimed is:

1. A process for the preparation of a compound of Formula IIA or Formula IIB:



II A II B

which comprises heating a compound of Formula IA or Formula IB



I A I B

wherein R_1 is C_{1-8}alkyl, cyclohexyl, phenyl, phenyl substituted with C_{1-6}alkyl, halo, nitro, C_{1-6}alkoxy, C_{1-6}alkylmercapto or CF_3, napthyl or napthyl substituted with C_{1-6}alkyl, halo, nitro, C_{1-6}alkoxy or CF_3;

R_2 is C_{1-8}alkyl, C_{1-8}alkenyl cyclohexyl, phenyl, or phenyl C_{1-6}alkyl wherein each phenyl may be substituted with one or two substituents selected from nitro, C_{1-6}alkoxy methylenedioxy or CF_3; and

R_3 is C_{1-12}alkyl, C_{1-8}alkenyl, C_{3-6}cycloalkyl, phenyl or phenyl C_{1-6}alkyl wherein each phenyl may be substituted with one or two substituents selected from nitro, C_{1-6}alkyl, halo, nitro, C_{1-6}alkoxyl, methylenedioxy, CF_3 or dialkylamino,

and urea together in the presence of a non-volatile ammonium salt.

2. A process of claim 1 wherein R_1 is phenyl or substituted phenyl.

3. A process of claim 2 wherein R_2 is alkyl.

4. A process of claim 3 wherein R_3 is alkyl.

5. A process of claims 1-4 wherein the process is carried out at a temperature of 75-190°C.

6. A process of claim 5 wherein Formula IA is L-ephedrine.

7. A process of claim 6 wherein the process is carried out at 160-190°C.

8. A process for the preparation of (4R,5S)-1,5-dimethyl-4-phenylimidizolidin-2-one which comprises heating about one equivalent L-ephedrine with three equivalents urea and one equivalent ammonium sulfamate at 175-179°C.

9. A process for the preparation of (4S,5R)-1,5-dimethyl-4-phenyl-imidizolidin-2-one which comprises heating about one equivalent D-ephedrine with three equivalents urea and one equivalent ammonium sulfamate at 165-180°C.

10. The compound (4R,5S)-1,5-dimethyl-4-phenylimidizolidine-2-one or (4S,5R)-1,5-dimethyl-4-phenylimidizolidin-2-one when prepared by the process of claims 1-9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18691

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 233/02
US CL :548/322.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/322.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DREWES et al. Ephedrine-derived Imidazolidin-2ones. Broad Utility Chiral Auxiliaries in Asymmetric Synthesis. Chem. Ber. 1993, Vol. 126, No. 12, pages 2663-2673. See scheme 1, page 2663.	1-4, 8-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 SEPTEMBER 2000	Date of mailing of the international search report 04 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer TAOFIQ A. SOLOLA Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18691

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-7
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.